California Institute for Regenerative Medicine

Mitochondrial DNA variant associated with Leber hereditary optic neuropathy and high-altitude Tibetans.

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Public Summary:

Scientific Abstract:
The distinction between mild pathogenic mtDNA mutations and population polymorphisms can be ambiguous because both are homoplasmic, alter conserved functions, and correlate with disease. One possible explanation for this ambiguity is that the same variant may have different consequences in different contexts. The NADH dehydrogenase subunit 1 (ND1) nucleotide 3394 T > C (Y30H) variant is such a case. This variant has been associated with Leber hereditary optic neuropathy and it reduces complex I activity and cellular respiration between 7% and 28% on the Asian B4c and F1 haplogroup backgrounds. However, complex I activity between B4c and F1 mtDNAs, which harbor the common 3394T allele, can also differ by 30%. In Asia, the 3394C variant is most commonly associated with the M9 haplogroup, which is rare at low elevations but increases in frequency with elevation to an average of 25% of the Tibetan mtDNAs (odds ratio = 23.7). In high-altitude Tibetan and Indian populations, the 3394C variant occurs on five different macrohaplogroup M haplogroup backgrounds and is enriched on the M9 background in Tibet and the C4a4 background on the Indian Deccan Plateau (odds ratio = 21.9). When present on the M9 background, the 3394C variant is associated with a complex I activity that is equal to or higher than that of the 3394T variant on the B4c and F1 backgrounds. Hence, the 3394C variant can either be deleterious or beneficial depending on its haplogroup and environmental context. Thus, this mtDNA variant fulfills the criteria for a common variant that predisposes to a "complex" disease.

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